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EXAMINER	
XIE, XIAOZHEN	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,606	BRUNKOW ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *89 and 91-109* is/are pending in the application.

4a) Of the above claim(s) *97-100 and 107-109* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *89,91-96 and 101-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20081230*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *genetic codon table*.

DETAILED ACTION

Response to Amendment

The Information Disclosure Statement (IDS) filed 30 December 2008 has been entered. The Terminal Disclaimer filed 21 November 2008 is acknowledged. Applicant's amendment of the claims filed on 21 November 2008 has been entered.

In the office action mailed 31 July 2008, claim 89 is indicated allowable. Upon further review, it appears that the claim is subject to new grounds of rejection as the following.

Claims 1-88 and 90 are cancelled. Claims 89 and 91-109 are pending. Claims 97-100 and 107-109 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 89, 91-96 and 101-106 are under examination.

Claim Rejections Withdrawn

The rejection of claims 88, 91-96 and 101-106 under 35 U.S.C. § 112, first paragraph, as failing to comply the enablement requirement, is withdrawn in response to Applicant's cancellation of the independent claim 88 and amendment of the independent claim 101 to recite "the polypeptide encoded by SEQ ID NO: 1".

The rejection of claims 101 and 103-106 under 35 U.S.C. 102(e), as being anticipated by Queen et al. (US 6,180,370 B1), is withdrawn in response to Applicant's amendment of the claim to limit the polypeptide binds to the polypeptide encoded by SEQ ID NO: 1.

Claim Rejections Maintained

Double Patenting

Claims 89 and 91-96 remain rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-8 of U. S. Patent No: 6,803,453 for reasons set forth in the previous office actions.

Applicant submitted a Terminal Disclaimer on 21 November 2008 to obviate the rejection. However, the Terminal Disclaimer is defective, specifically, the U. S. Patent No: 6,804,453 is incorrect, and it should be "6,803,453".

New Grounds of Rejection

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 101 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Because it does not require that the polypeptide be isolated, they encompass products of nature, which are not patentable. This rejection could be overcome by addition of the limitation wherein the polypeptide is isolated.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 89, 91-96 and 101-106 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to:

(1) an isolated antibody or antigen binding fragment thereof which specifically binds to a polypeptide encoded by a polynucleotide having at least 90% identity to a polynucleotide sequence selected from the group consisting of SEQ ID NOS: 1, 5, 9, 11, 13 and 15, wherein said polypeptide retains a cysteine backbone comprising eight cysteines and retains the ability to decrease bone mineral content, and wherein the antibody or antigen binding fragment thereof has an affinity of at least 10^{-7} M or 10^{-8} M; a hybridoma producing the antibody; and a polypeptide comprising the antibody or an antibody fragment thereof; and

(2) a polypeptide comprising an antibody or an antibody fragment thereof, wherein the polypeptide binds to the polypeptide encoded by SEQ ID NO: 1 with an affinity of $K_a \geq 10^7$ M^{-1}.

The claims encompass a large genus of antibodies. The claim language reads on antibodies that bind to any polypeptide encoded by a polynucleotide having at least 90% identity to the recited SEQ ID NOs, and the polypeptide has a cysteine backbone comprising 8 cysteines and has the ability to decrease bone mineral content. For

example, in the case of human BEER, the encoding polynucleotide of SEQ ID NO: 1 has 2301 nucleotides or base pairs, and a variation of 10% in sequence would allow a total of 230 nucleotide/base pair changes. While certain changes in a coding sequence would not alter the encoded amino acids due to the degenerating nature of a codon, however, changes of the first nucleotide of a codon would alter the encoded amino acid. For example, both UU**U** and UU**C** are codons for Phe; however, **C**UU, **A**UU and **G**UU are codons for Leu, Ile and Val, respectively (see attached codon table). The claims have no limitation with regards to where the changes would be in the polynucleotide sequence. Therefore, the claim language allows a maximum of 230 residue changes, which means that the polypeptide need to have nearly no homology to the polypeptide of SEQ ID NO: 2 (the human BEER which has 213 amino acids), and all that is required is the cysteine backbone and the functional activity of decreasing bone mineral content.

In addition, claim 101 and the depending claims are not limited to antibody or antibody fragment thereof conjugated to an effector or receptor molecule. The claims encompass any polypeptide comprising an antibody or antibody fragment (e.g., an Fc domain) that is capable of binding to the polypeptide encoded by SEQ ID NO: 1. The claimed polypeptides can be antibodies directed to the polypeptide, but can also be any interacting proteins or binding ligands/receptors of the polypeptide encoded by SEQ ID NO: 1. Applicant has not described the nature of these molecules, and no identifying characteristics is disclosed in the specification.

What Applicant has disclosed in the specification are antibodies for the TGF-binding-proteins, i.e., the SOST or BEER proteins (commonly known as sclerostin),

which are encoded by the polynucleotide sequences set forth in SEQ ID NOs: 1, 5, 7, 9, 11, 13 and 15, and have the amino acid sequences set forth in SEQ ID NOs: 2, 6, 8, 10, 12, 14 and 16. The specification discloses that these TGF- binding-proteins are capable to bind to BMPs and prevent its binding to the receptors, and therefore, may exhibit BMP antagonistic activity and decrease bone mineral content *in vivo*. Applicant discloses a human BEER (encoded by SEQ ID NO: 1) and two variants of human BEER (V10I and P38R encoded by SEQ ID NOs: 5 and 7, respectively), a vervet BEER (encoded by SEQ ID NO: 9), a mouse BEER (encoded by SEQ ID NO: 11), a rat BEER (encoded by SEQ ID NO: 13), and a bovine BEER (encoded by SEQ ID NO: 15). Applicant has not described the genus of the polypeptides that have the structure (i.e., the cysteine backbone) and the function (i.e., decreasing bone mineral content) characteristics. Without sufficient identifying characteristics for the polypeptides to which antibodies, antibody fragments thereof, or polypeptides bind to, the specification does not meet the written description requirement for the genus of the molecules. Thus, the claims encompass a genus of molecules, which vary substantially in composition, and could have very different structural and functional characteristics from that Applicant has disclosed.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor

present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of antibodies or antigen binding fragments thereof, which specifically bind to the polypeptide encoded by a polynucleotide having the sequence set forth in SEQ ID NO: 1, 5, 9, 11, 13 and 15, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483 (BPAI 1993). In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only antibodies or antigen binding fragments thereof, which specifically bind to the polypeptide encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO: 1, 5, 9, 11, 13 and 15, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 89, 91-96 and 101-106 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) an isolated antibody or antigen binding fragment thereof which specifically binds to the polypeptide encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO: 1, 5, 9, 11, 13 and 15, wherein said polypeptide retains a cysteine backbone comprising eight cysteines and retains the ability to decrease bone mineral content; and a hybridoma that produces the antibody; and

(2) an isolated antibody or antigen binding fragment thereof which binds to the polypeptide encoded by SEQ ID NO: 1 with an affinity of $K_a \geq 10^7\ M^{-1}$*, wherein the antibody or antigen binding fragment thereof further comprising an effector or receptor molecule,*

does not reasonably provide enablement for: (1) the genus of antibodies or antigen binding fragments thereof which specifically bind to a polypeptide encoded by a polynucleotide having at least 90% identity to a polynucleotide sequence selected from the group consisting of SEQ ID NOS: 1, 5, 9, 11, 13 and 15; (2) the genus of polypeptides comprising an antibody or an antibody fragment thereof, wherein the polypeptides bind to the polypeptide encoded by SEQ ID NO: 1 with an affinity of K_a $\geq 10^7$ M^{-1}. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

As stated above, the claims are broad and they encompass a large genus of molecules that Applicant has not provided sufficient disclosure for the identifying

characteristics of the genus, and has not provided sufficient guidance to make and use the genus of molecules.

First, by referencing a polypeptide encoded by a polynucleotide having at least 90% identity to the recited SEQ ID NOs, the claims allow a huge margin of variations for the polypeptide sequence. For example, the polynucleotide of SEQ ID NO: 1 (encoding human BEER) has 2301 nucleotides or base pairs, and a variation of 10% in polynucleotide sequence would allow a total of 230 nucleotide/base pair changes. While certain changes in a coding sequence would not alter the encoded amino acids due to the degenerating nature of a codon, however, changes of the first nucleotide of a codon would resulting a different amino acid. The claims have no limitation with regards to where the changes would be in the polynucleotide sequence. Therefore, the claim language allows a maximum of 230 residue changes, which means that the polypeptide need to have nearly no homology to the polypeptide of SEQ ID NO: 2 (the human BEER, which contains 213 amino acids), and all that is required is the cysteine backbone and the functional activity of decreasing bone mineral content. Applicant has not provided sufficient teachings with regards to the molecular identity for these polypeptides. Without knowing the antigen, one of ordinary skill in the art would not know how to make an antibody directed to the same.

Second, the recitation of “a polypeptide comprising an antibody, or an antibody fragment thereof, wherein the polypeptide binds to the polypeptide encoded by SEQ ID NO: 1” in claim 101 does not limit the polypeptide comprising an antibody or an antigen binding fragment thereof directed to the polypeptide encoded by SEQ ID NO: 1. The

claims encompass any polypeptide that is capable of binding to the polypeptide encoded by SEQ ID NO: 1, as long as the polypeptide is conjugated to an antibody fragment, such as an Fc domain. Thus, the claimed polypeptides can be antibodies directed to the polypeptide, but can also be any interacting proteins or binding ligands/receptors of the polypeptide encoded by SEQ ID NO: 1. Applicant has not described the nature of these molecules, and no identifying characteristics is disclosed in the specification.

Third, claims 101 and 102 recite "a polypeptide comprising an antibody, or an antibody fragment thereof". While antibody molecules are frequently linked to an auxiliary moiety, such as a toxin, label, enzyme, etc., and an immunoglobulin Fc domain is frequently used to conjugate with a polypeptide, in particular, for making multimeric protein, the art, however, does not teach "a polypeptide comprising an antibody". A polypeptide is a continuous chain of amino acids joined by peptide bonds, whereas an antibody contains four polypeptides, 2 heavy chains and 2 light chains joined by disulfide bonds. The specification fails to provide guidance how to make "a polypeptide (a chain of amino acids) comprising an antibody, or an antibody fragment thereof (a dimer or tetramer of polypeptide)".

What Applicant has disclosed in the specification are antibodies for the TGF-β binding-proteins, i.e., the SOST or BEER proteins (commonly known as sclerostin), which are encoded by the polynucleotide sequences set forth in SEQ ID NOs: 1, 5, 7, 9, 11, 13 and 15, and have the amino acid sequences set forth in SEQ ID NOs: 2, 6, 8, 10, 12, 14 and 16. The specification discloses that these TGF-β binding-proteins are

capable to bind to BMPs and prevent its binding to the receptors, and therefore, may exhibit BMP antagonistic activity and decrease bone mineral content *in vivo*. Applicant discloses a human BEER (encoded by SEQ ID NO: 1) and two variants of human BEER (V10I and P38R encoded by SEQ ID NOs: 5 and 7, respectively), a vervet BEER (encoded by SEQ ID NO: 9), a mouse BEER (encoded by SEQ ID NO: 11), a rat BEER (encoded by SEQ ID NO: 13), and a bovine BEER (encoded by SEQ ID NO: 15). Applicant has not disclosed the genus of the polypeptides that have the structure (i.e., the cysteine backbone) and the function (i.e., decreasing bone mineral content) characteristics. Without sufficient identifying characteristics, one of ordinary skill in the art would not know how to make and use the broadly claimed molecules, and the enablement requirement sets forth in the 35 U.S.C. 112, first paragraph, is not met.

Due to the large quantity of experimentation necessary to generate the nearly infinite number of polypeptides recited in the claims, and generate antibodies or antigen binding fragments thereof directed to same, and screen the polypeptides and the antibodies for physiological activity, the lack of direction/guidance presented in the specification, the absence of working examples, the complex nature of the invention, the state of the art which establishes the unpredictability of the effects of protein structure on function, and the breadth of the claims which fails to recite sufficient structural limitations for the genus, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 89, 91-96 and 102 are rejected under 35 U.S.C. 102(a) as being anticipated by Valenzuela et al (WO 98/49296, International Pub. Date: 5 November 1998).

WO 98/49296 teaches antibodies (polyclonal, monoclonal and chimeric antibodies) that specifically bind to a polypeptide of human Cerberus (see claims and pp. 14, lines 16-24), as well as hybridomas that produce the antibodies (pp. 14, lines 6-14). WO 98/49296 teaches that human Cerberus contains eight cysteines that are involved in the disulfide bond formation, e.g., at positions 162, 176, 186, 190, 209, 223, 239 and 241 (ses SEQ ID NO: 2 of WO 98/49296). WO 98/49296 teaches has the ability to antagonizing bone morphogenic protein (see Abstract).

While WO 98/49296 does not explicitly teach that the human Cerberus is encoded by a polynucleotide having at least 90% identity to a polynucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 5, 9, 11, 13 and 15, the amino acid sequence of human Cerberus, however, meets the limitation of the polypeptide encoded by a polynucleotide having at least 90% identity to a polynucleotide sequence

selected from the group consisting of SEQ ID NOs: 1, 5, 9, 11, 13 and 15 (see office action under section under 35 U.S.C. 112, first paragraph, *supra*). In other words, the polypeptide is the product of the polynucleotide through codon translation. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (see MPEP 2113 [R-1]).

While WO 98/49296 does not explicitly disclose the affinity Ka recited in claims 94, 95, e.g., at least 10^{-7} M or 10^{-8} M, WO 98/49296, however, teaches purifying antibodies using immunoabsorption, immunoaffinity chromatography, HPLC, or a combination thereof (pp. 15, lines 13-23). Thus, it would be expected that the antibodies of the prior art would exhibit the required affinity. Furthermore, since the product of the prior art is identical to that required by the claims, it will inherently possess the property. A compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)), as are their processes and yields (*In re Von Schickh,* 362 F.2d 821, 150 USPQ 300 (CCPA 1966)). Furthermore, measuring antibody affinity has been taught by Azimzadeh et al. (J. Mol. Recog., 1990, Vol. 3(3):108-116), which teaches immunoaffinity purified antibodies have at least an affinity of 10^{-7} M or 10^{-8} M. Thus, the Azimzadeh et al. constitute further evidence of the inherency of the affinity constant.

For these reasons, WO 98/49296 anticipates the instant claims.

Claims 101 and 103-106 are rejected under 35 U.S.C. 102(e) as being anticipated by Rueger et al. (U. S. Patent No: 6,949,505 B1, which was filed on 18 August 1994).

Rueger et al. teach the use of morphogens, e.g., human BMP-6, for promoting neuron dendrite outgrowth (see claims). Rueger et al. teach that the morphogen can be associated with molecules capable of targeting the morphogen to nerve tissue, for example, an antibody, antibody fragment, or other binding protein that interacts specifically with a surface molecule on nerve tissue cells (col. 35, lines 23). BMP-6 binds to the sclerostin (polypeptide encoded by SEQ ID NO: 1 of the instant application) *in vivo*, as evidenced by Winkler et al. (EMBO J., 2003, Vol. 22(23):6267-76), and inherently has the recited binding affinity. Rueger et al. also teach that the morphogen may be modified to render it more lipophilic, or it may be conjugated to another molecule which is naturally transported across the barrier (col. 13, lines 16-22). Therefore, Rueger et al. anticipate the instant claims.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached 571-272-0835. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
March 16, 2009

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646